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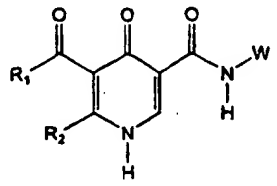
(54) Title: SUBSTITUTED 1,4-DIHYDRO-4-OXONICOTINIC CARBOXAMIDES: GABA BRAIN RECEPTOR LIGANDS



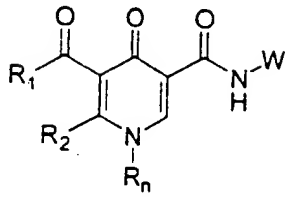
(a)

(57) Abstract

Disclosed are compounds of formula (a), or the pharmaceutically acceptable non-toxic salts thereof wherein: R_1 is lower alkyl; R_2 is hydrogen or lower alkyl; or R_1 and R_2 together represent a 2, 3, or 4 carbon alkylene moiety that together with the pyridone ring to which they are attached form a 5, 6 or 7 membered carbocyclic ring; and W is (un)substituted lower alkyl, aryl, arylalkyl, or heteroaryl; or W is NR_3COR_4, COR_4, $CONR_3R_4$ or CO_2R_4 where R_3 and R_4 are the same or different and represent hydrogen or lower alkyl, which compounds are highly selective agonists, antagonists or inverse agonists for GABAa brain receptors or prodrugs of agonists, antagonists or inverse agonists for GABAa brain receptors. These compounds are useful in the diagnosis and treatment of anxiety, sleep, cognitive and seizure disorders, and overdose with benzodiazepine drugs and for enhancement of alertness.

WHAT IS CLAIMED IS:

1. A compound of the formula:



or the pharmaceutically acceptable non-toxic salts thereof wherein:

R_1 is lower alkyl;

R_2 is hydrogen or lower alkyl; or

R_1 and R_2 together represent a 2, 3, or 4 carbon alkylene moiety that together with the pyridone ring to which they are attached form a 5, 6, or 7 membered oxo-substituted carbocyclic ring where each carbon atom of said alkylene moiety is optionally substituted with hydroxy, halogen, C1-C6 alkyl, amino, C1-C6 alkoxy, or trifluoromethyl; and

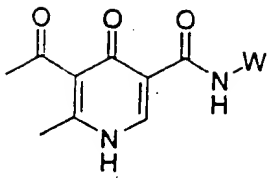
W is lower alkyl optionally substituted with one or two groups selected from halogen, hydroxy, lower alkoxy, amino, or mono- or dialkyl amino where each alkyl portion is independently lower alkyl; or

W is aryl, arylalkyl, or heteroaryl, where the ring portion of each is optionally substituted with one or two groups independently selected from halogen, trifluoromethyl, cyano, hydroxy, lower alkyl, lower alkoxy, amino, mono- or dialkylamino where each alkyl portion is lower alkyl, methylaminoalkyl where each alkyl portion is lower alkyl, or

$$NR_3\text{-}\overset{O}{\overset{\|}{C}}\text{-}R_4 \;,\; \overset{O}{\overset{\|}{C}}\text{-}R_4 \;,\; \overset{O}{\overset{\|}{C}}NR_3R_4 \;,\; CO_2R_4$$

where R_3 and R_4 are the same or different and represent hydrogen or lower alkyl.

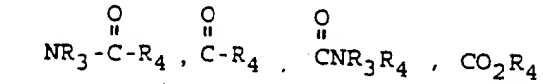
2. A compound according to claim 1 of the formula:



or the pharmaceutically acceptable non-toxic salts thereof wherein:

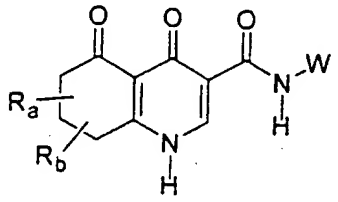
W is lower alkyl optionally substituted with one or two groups selected from halogen, hydroxy, lower alkoxy, amino, or mono- or dialkyl amino where each alkyl portion is independently lower alkyl; or

W is aryl, arylalkyl, or heteroaryl, where the ring portion of each is optionally substituted with one or two groups independently selected from halogen, trifluoromethyl, cyano, hydroxy, lower alkyl, lower alkoxy, amino, mono or dialkylamino where each alkyl portion is lower alkyl, methylaminoalkyl where each alkyl portion is lower alkyl, or



where R_3 and R_4 are the same or different and represent hydrogen or lower alkyl.

3. A compound according to claim 1 of the formula:



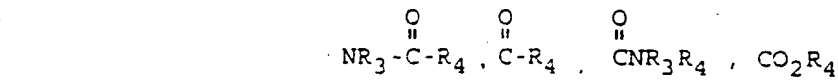
or the pharmaceutically acceptable non-toxic salts thereof wherein:

R_a is hydrogen, halogen, hydroxy, C_1-C_6 alkyl, C_1-C_6 alkoxy, amino, mono- or di(C_1-C_6)alkylamino, or trifluoromethyl;

R_b is halogen, hydroxy, C_1-C_6 alkyl, C_1-C_6 alkoxy, amino, mono- or di(C_1-C_6)alkylamino, or trifluoromethyl;

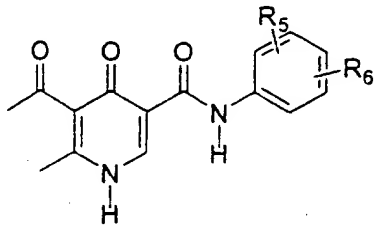
W is lower alkyl optionally substituted with one or two groups selected from halogen, hydroxy, lower alkoxy, amino, or mono- or dialkyl amino where each alkyl portion is independently lower alkyl; or

W is aryl, arylalkyl, or heteroaryl, where the ring portion of each is optionally substituted with one or two groups independently selected from halogen, trifluoromethyl, cyano, hydroxy, lower alkyl, lower alkoxy, amino, mono- or dialkylamino where each alkyl portion is lower alkyl, methylaminoalkyl where each alkyl portion is lower alkyl, or



where R_3 and R_4 are the same or different and represent hydrogen or lower alkyl.

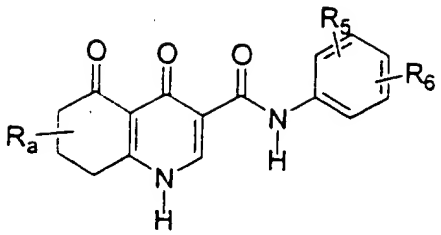
4. A compound according to claim 1 of the formula:



or the pharmaceutically acceptable non-toxic salts thereof wherein:

R_5 and R_6 are the same or different and represent hydrogen, halogen, hydroxy, lower alkyl, lower alkoxy, amino, mono or dialkylamino where each alkyl portion is lower alkyl, or methylaminoalkyl where each alkyl portion is lower alkyl.

5. A compound according to claim 1 of the formula:

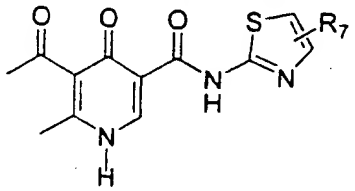


or the pharmaceutically acceptable non-toxic salts thereof wherein:

R_a is hydrogen, halogen, hydroxy, C_1-C_6 alkyl, C_1-C_6 alkoxy, amino, mono- or di(C_1-C_6)alkylamino, or trifluoromethyl;

R_5 and R_6 are the same or different and represent hydrogen, halogen, hydroxy, lower alkyl, lower alkoxy, amino, mono or dialkylamino where each alkyl portion is lower alkyl, or methylaminoalkyl where each alkyl portion is lower alkyl.

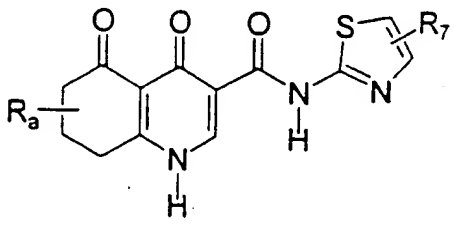
6. A compound according to claim 1 of the formula:



or the pharmaceutically acceptable non-toxic slats thereof wherein:

R_7 is hydrogen, halogen, hydroxy, lower alkyl, lower alkoxy, amino, mono or dialkylamino where each alkyl portion is lower alkyl, or methylaminoalkyl where each alkyl portion is lower alkyl.

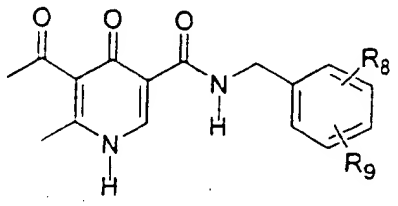
7. A compound according to claim 1 of the formula:



or the pharmaceutically acceptable non-toxic salts thereof wherein:

R_7 is hydrogen, halogen, hydroxy, lower alkyl, lower alkoxy, amino, mono or dialkylamino where each alkyl portion is lower alkyl, or methylaminoalkyl where each alkyl portion is lower alkyl.

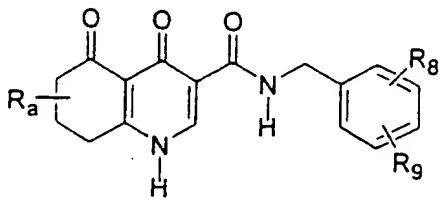
8. A compound according to claim 1 of the formula:



or the pharmaceutically acceptable non-toxic salts thereof wherein:

R_8 and R_9 are the same or different and represent hydrogen, halogen, cyano, hydroxy, lower alkyl, lower alkoxy, amino, mono or dialkylamino where each alkyl portion is lower alkyl, methylaminoalkyl where each alkyl portion is lower alkyl.

9. A compound according to claim 1 of the formula:



or the pharmaceutically acceptable non-toxic salts thereof wherein:

R_8 and R_9 are the same or different and represent hydrogen, halogen, cyano, hydroxy, lower alkyl, lower alkoxy, amino, mono or dialkylamino where each alkyl portion is

lower alkyl, methylaminoalkyl where each alkyl portion is lower alkyl.

10. A compound according to claim 1 which is N-(2-fluorophenyl)-1,4-dihydro-4-oxo-5-acetyl-6-methyl nicotinic-3-carboxamide.

11. A compound according to claim 1 which is N-(4-methoxyphenyl)-1,4-dihydro-4-oxo-5-acetyl-6-methyl nicotinic-3-carboxamide.

12. A compound according to claim 1 which is N-(4-methoxy-2-pyridyl)-1,4-dihydro-4-oxo-5-acetyl-6-methyl nicotinic-3-carboxamide.

13. A compound according to claim 1 which is N-(4-(±)-(1-methylaminoethyl)benzyl)-1,4-dihydro-4-oxo-5-acetyl-6-methyl nicotinic-3-carboxamide.

14. A compound according to claim 1 which is N-(n-Butyl)-1,4,5,6,7,8-hexahydroquinoline-4,5-dione-nicotinic-3-carboxamide.

15. A compound according to claim 1 which is N-(4-ethoxyphenyl)-1,4-dihydro-4-oxo-5-acetyl-6-methyl nicotinic-3-carboxamide.

16. A compound according to claim 1 which is N-(3-fluorophenyl)-1,4-dihydro-4-oxo-5-acetyl-6-methyl nicotinic-3-carboxamide.

17. A compound according to claim 1 which is N-(2-fluoro-4-methoxyphenyl)-1,4-dihydro-4-oxo-5-acetyl-6-methyl nicotinic-3-carboxamide.

18. A compound according to claim 1, which is: N-(3-tolyl)-1,4-dihydro-4-oxo-5-acetyl-6-methyl nicotinic-3-carboxamide.

19. A compound according to claim 1 which is N-(2,4-difluorophenyl)-1,4-dihydro-4-oxo-5-acetyl-6-methyl nicotinic-3-carboxamide.

20. A compound according to claim 1 which is N-(2,6-difluorophenyl)-1,4-dihydro-4-oxo-5-acetyl-6-methyl nicotinic-3-carboxamide.

21. A compound according to claim 1 which is N-(benzyl)-1,4-dihydro-4-oxo-5-acetyl-6-methyl nicotinic-3-carboxamide.

22. A compound according to claim 1 which is N-(2-methoxyphenyl)-1,4-dihydro-4-oxo-5-acetyl-6-methyl nicotinic-3-carboxamide.

23. A compound according to claim 1 which is N-(3-methylaminomethylphenyl)-1,4-dihydro-4-oxo-5-acetyl-6-methyl nicotinic-3-carboxamide.

24. A compound according to claim 1 which is N-(2-fluorobenzyl)-1,4-dihydro-4-oxo-5-acetyl-6-methyl nicotinic-3-carboxamide.

25. A compound according to claim 1 which is N-(2,3-difluorobenzyl)-1,4-dihydro-4-oxo-5-acetyl-6-methyl nicotinic-3-carboxamide.

26. A compound according to claim 1 which is N-(isoamyl)-1,4-dihydro-4-oxo-5-acetyl-6-methyl nicotinic-3-carboxamide.

27. A compound according to claim 1 which is N-(4-chlorobenzyl)-1,4-dihydro-4-oxo-5-acetyl-6-methyl nicotinic-3-carboxamide.

28. A compound according to claim 1 which is N-(phenyl)-1,4,5,6,7,8-hexahydroquinoline-4,5-dione-nicotinic-3-carboxamide.

29. A compound according to claim 1 which is N-(2-fluorophenyl)-1,4,5,6,7,8-hexahydroquinoline-4,5-dione-nicotinic-3-carboxamide.

30. A compound according to claim 1 which is N-(2-thiazolyl)-1,4,5,6,7,8-hexahydroquinoline-4,5-dione-nicotinic-3-carboxamide.

31. A compound according to claim 1 which is N-(benzyl)-1,4,5,6,7,8-hexahydroquinoline-4,5-dione-nicotinic-3-carboxamide.

32. A compound according to claim 1 which is N-(2-fluorobenzyl)-1,4,5,6,7,8-hexahydroquinoline-4,5-dione-nicotinic-3-carboxamide.

33. A compound according to claim 1 which is N-(4-methoxybenzyl)-1,4,5,6,7,8-hexahydroquinoline-4,5-dione-nicotinic-3-carboxamide.

34. A compound according to claim 1 which is N-(phenyl)-1,4-dihydro-4-oxo-5-acetyl-6-methyl nicotinic-3-carboxamide.

35. A compound according to claim 1 which is N-(Butyl)-1,4-dihydro-4-oxo-5-acetyl-6-methyl nicotinic-3-carboxamide.

36. A compound according to claim 1 which is N-(2(4-Methylthiazoleyl))-1,4-dihydro-4-oxo-5-acetyl-6-methyl nicotinic-3-carboxamide.

37. A compound according to claim 1 which is N-(2-(4-methoxy)pyridyl)-1,4,5,6,7,8-hexahydroquinoline-4,5-dione-nicotinic-3-carboxamide.

38. A compound according to claim 1 which is N-(2-thiazolyl)-1,4,5,6,7,8-hexahydroquinoline-4,5-dione-nicotinic-3-carboxamide.